O40—H402···O1^{ii}	0.88 (2)	1.78 (2)	2.659 (1)	176 (2)
O50—H501···O60	0.82 (2)	1.94 (2)	2.755 (1)	174 (2)
O50—H502···O70	0.81 (2)	1.92 (2)	2.726 (1)	170 (2)
O60—H601···O2^{iv}	0.82 (2)	1.90 (2)	2.718 (1)	172 (2)
O60—H602···O50^{v}	0.84 (3)	1.98 (3)	2.812 (1)	178 (3)
O70—H701···O40	0.80 (2)	2.09 (2)	2.861 (1)	165 (2)
O70—H702···O60^{ii}	0.85 (2)	1.95 (2)	2.790 (1)	171 (2)

Symmetry codes: (i) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (ii) $1+x, y, z$; (iii) $2-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iv) $\frac{1}{2}+x, \frac{1}{2}-y, 2-z$; (v) $x-\frac{1}{2}, \frac{1}{2}-y, 2-z$.

The data collection nominally covered over a hemisphere of reciprocal space, by a combination of five sets of exposures, two with the detector set at $2\theta = 30°$ and three with $2\theta = 55°$. Each set had a different φ angle for the crystal and each exposure covered 0.6° in ω. The crystal-to-detector distance was 4.97 cm. No intensity decay was observed. Coverage of the unique set was over 99% complete to at least 70° in 2θ. H atoms bonded to O or N atoms were located by difference Fourier calculations and refined isotropically; other H atoms were placed geometrically and refined with a riding model (including free rotation about C—C bonds for methyl groups), but with the C—H distances free to refine. All H atoms connected to the same C atom were given the same shifts. U_{iso} values were constrained to be $1.2U_{eq}$ of the carrier atom, except that a free variable for U_{iso} was refined for each methyl group.

Data collection: *SMART* (Siemens, 1995). Cell refinement: *SAINT* (Siemens, 1995). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL*. Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

The purchase of the Siemens SMART diffractometer was made possible through support from The Research Council of Norway (NFR).

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: AB1443). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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5,7-Dichlorokynurenic Acid Hydrate, an Antagonist for the Glycine Binding Site on the NMDA Receptor

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Abstract

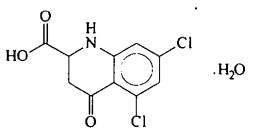
The structure of 5,7-dichlorokynurenic acid hydrate (IUPAC name: 5,7-dichloro-4-oxo-1,4-dihydro-2-quinolinecarboxylic acid hydrate), $C_{10}H_5Cl_2NO_3.H_2O$, has been determined by X-ray analysis. The molecule exists as a keto tautomer. All hydrogen-bond donors and acceptors take part in the hydrogen-bonding network which connects molecules into a three-dimensional array. Graph-set analysis shows that there are both rings and chains in the network; however, there are no carboxylic acid dimers. The O—H portion of the carboxylic acid group is in a *trans* orientation with respect to the N—H group of the bicyclic ring system; the plane of the carboxylic group makes an angle of 7.6 (2)° with the plane of the heterocyclic ring.

Comment

There is increasing evidence that the amino acid glycine acts as an endogenous co-agonist at a specific strychnine-insensitive site on the NMDA (*N*-methyl-D-aspartate) receptor of the excitatory amino acid receptor

complex (Johnson & Ascher, 1987; Kleckner & Dingledine, 1988). The occupation of the glycine site by an antagonist is regarded as a requirement for receptor activation and, consequently, this site plays a physiological role in the modulation of synaptic responses mediated by the NMDA receptor (Kemp & Leeson, 1993). Therefore, the role of the agonists and antagonists acting at the glycine site is crucial for the development of potent therapies in numerous central nervous system disorders. Soon after the discovery of the modulatory action of glycine, kynurenic acid was found to possess glycine/NMDA antagonist activity (Watson, Hood, Monahan & Lanthorn, 1988; Birch, Grossman & Hayes, 1988). Further studies (Leeson *et al.*, 1991) revealed that more potent and more selective antagonists can be obtained by hydrophobic substitutions on the benzene ring fragment of kynurenic acid.

We report here the results of the X-ray crystallographic studies of one of the most potent compounds in the series, namely, 5,7-dichlorokynurenic acid (which crystallizes as a hydrate), (I). The IC_{50} value (IC_{50} is the concentration required to achieve 50% inhibition of the binding of [^{3}H] glycine to its receptor binding site) against [^{3}H] glycine binding to rat cortical membranes is 200 nM, which shows a 200-fold increase compared with kynurenic acid itself. Also, the selectivity has improved dramatically; for 5,7-dichlorokynurenic acid, the IC_{50} value against glycine binding is 375, 500 and 1500 times greater than for AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid), L-glutamate and kainic acid, respectively, while the respective values for kynurenic acid are 2.5, 4.5, and 24.



(I)

There is an extensive network of hydrogen bonds in the crystal structure in which all strong hydrogen bond donors and acceptors are involved. Interestingly, there is no carboxylic acid dimer but there are hydrogen-bonded dimers connected by intermolecular N1—H1···O21 bonds between the molecules connected by the *c* glide plane. A similar pattern was observed in another group of NMDA-receptor glycine site antagonists, 1,4-dihydro-2,3-quinoxalinediones (Kubicki, Kindopp, Capparelli & Codding, 1996). The other hydrogen bonds involve water molecules; the carboxylic OH group makes a very strong hydrogen bond with the O atom of a water molecule and both H atoms of a water molecule take part in hydrogen bonds with the keto-O atoms, O4 of two different molecules. There is also a relatively strong C8—H8···O21 interaction. The hydrogen-bonding data are presented in Table 2 and the hydrogen-bonding network is shown in Fig. 1. Using graph-set notation (Etter, MacDonald & Bernstein, 1990; Bernstein, Davis, Shimoni & Chang, 1995) for the description of the hydrogen-bond network, the first-level graph consists of one ring and three dimeric hydrogen bonds, $DDDR_2^2(10)$. At the second level, there are two new rings, closed by two 5,7-dichlorokynurenic acid molecules and two water molecules, and the first infinite chain which is made of alternate O22—H22···O1*W* and O1W—H1*W*1···O4 hydrogen bonds: $R_4^2(8)R_4^4(18)C_2^2(9)$. This structure possesses all of the features of the hydrogen-bond network postulated for the biological activity of 1,4-dihydro-2,3-quinoxalinediones (Kubicki, Kindopp, Capparelli & Codding, 1996). The difference in the size of the rings and chains is caused by a different disposition of hydrogen-bond donors and acceptors.

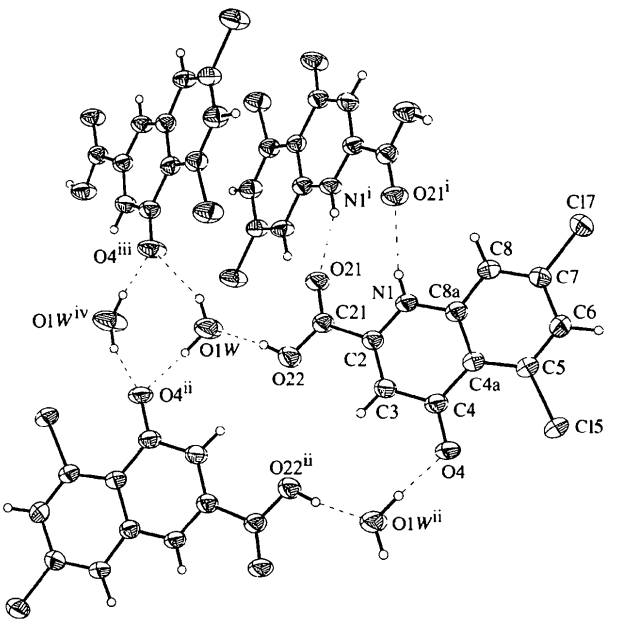


Fig. 1. The hydrogen-bonding scheme and atomic labelling scheme for the title compound. The ellipsoids are drawn at the 50% probability level and the H atoms are drawn as spheres of arbitrary radii. The hydrogen bonds are depicted as dashed lines. [Symmetry codes: (i) $1-x, y, \frac{1}{2}-z$; (ii) $\frac{1}{2}-x, \frac{1}{2}-y, 1-z$; (iii) $-\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$; (iv) $-x, y, \frac{1}{2}-z$.]

There is also a weak π-stacking interaction in the crystal structure; the distance between the mean planes of the molecules at (x, y, z) and $(1-x, -y, 1-z)$ is 3.45 (1) Å. However, this distance is quite long and the stacking covers approximately 20% of the plane, so hydrogen bonds seem to play the decisive role in the determination of crystal packing.

The bicyclic ring system is approximately planar, with the largest deviation from the least-squares plane being 0.022 (2) Å and the dihedral angle between the planes of the two six-membered rings being 1.42 (8)°. Both Cl atoms and the O4 atom are almost perfectly

coplanar with the plane of the bicyclic system, while the C21 atom is significantly out of this plane, with a deviation of 0.118 (3) Å. The plane of the carboxylic acid group makes an angle of 7.6 (2)° with the plane of the heterocyclic ring.

The molecule exists in the solid state as the keto tautomer. The bond lengths and angles pattern is typical, with the usual influence of the substituents on the intra-annular bond angles. The orientation of the OH portion of the carboxylic acid group is *trans* with respect to the N—H group; this disposition is probably enforced by a weak electrostatic interaction between the N—H group and O21 atom, which is suggested by the asymmetry of the bond angles N1—C2—C21 and C3—C2—C21 of 113.4 (2) and 124.9 (2)°, respectively. The asymmetry of the bond angles around the C4 and C5 atoms is caused by the repulsion between O4 and Cl5 which are separated by 2.894 (2) Å.

Experimental

The title compound was provided by Marion Merrell Dow Research Institute, Cincinnati, Ohio, USA, and recrystallized from ethanol by slow evaporation.

Crystal data

$C_{10}H_5Cl_2NO_3.H_2O$
M_r = 276.07
Monoclinic
$C2/c$
a = 12.5928 (7) Å
b = 10.6943 (10) Å
c = 16.0674 (5) Å
β = 93.168 (3)°
V = 2160.5 (2) Å^3
Z = 8
D_x = 1.697 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 14–41°
μ = 5.470 mm^{-1}
T = 293 (2) K
Block
0.3 × 0.3 × 0.2 mm
Colorless

Data collection

Enraf–Nonius CAD-4F diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North, Phillips & Mathews, 1968)
T_{min} = 0.307, T_{max} = 0.335
2201 measured reflections
2110 independent reflections

1890 reflections with $I > 2\sigma(I)$
R_{int} = 0.0201
θ_{max} = 74.86°
$h = 0 \rightarrow 14$
$k = 0 \rightarrow 6$
$l = -20 \rightarrow 19$
3 standard reflections
frequency: 33 min
intensity decay: 2%

Refinement

Refinement on F^2
$R(F)$ = 0.0406
$wR(F^2)$ = 0.1400
S = 1.229
2109 reflections
182 parameters
All H atoms refined

$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.574 e Å^{-3}
$\Delta\rho_{min}$ = −0.280 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.0008 (2)

$w = 1/[\sigma^2(F_o^2) + (0.0595P)^2 + 2.0735P]$
where $P = (F_o^2 + 2F_c^2)/3$

Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

N1—C2	1.344 (3)	C4a—C8a	1.409 (3)
N1—C8a	1.372 (3)	C4a—C5	1.423 (3)
C2—C3	1.354 (3)	C5—C6	1.368 (4)
C2—C21	1.504 (3)	C5—Cl5	1.734 (2)
C21—O21	1.200 (3)	C6—C7	1.393 (4)
C21—O22	1.300 (3)	C7—C8	1.368 (4)
C3—C4	1.447 (3)	C7—Cl7	1.729 (3)
C4—O4	1.246 (3)	C8—C8a	1.405 (3)
C4—C4a	1.469 (3)		
C2—N1—C8a	122.2 (2)	C5—C4a—C4	125.2 (2)
N1—C2—C3	121.7 (2)	C6—C5—C4a	122.3 (2)
N1—C2—C21	113.4 (2)	C6—C5—Cl5	115.4 (2)
C3—C2—C21	124.9 (2)	C4a—C5—Cl5	122.3 (2)
O21—C21—O22	125.3 (2)	C5—C6—C7	119.4 (2)
O21—C21—C2	120.6 (2)	C8—C7—C6	122.0 (2)
O22—C21—C2	114.1 (2)	C8—C7—Cl7	118.8 (2)
C2—C3—C4	121.4 (2)	C6—C7—Cl7	119.3 (2)
O4—C4—C3	120.5 (2)	C7—C8—C8a	117.8 (2)
O4—C4—C4a	123.9 (2)	N1—C8a—C8	117.1 (2)
C3—C4—C4a	115.6 (2)	N1—C8a—C4a	119.8 (2)
C8a—C4a—C5	115.4 (2)	C8—C8a—C4a	123.1 (2)
C8a—C4a—C4	119.4 (2)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O21^{i}	0.82 (3)	2.08 (3)	2.867 (3)	159 (3)
O22—H22···O1W	0.85 (4)	1.70 (4)	2.549 (3)	171 (4)
O1W—H1W1···O4^{ii}	0.88 (5)	2.11 (5)	2.931 (3)	154 (4)
O1W—H1W2···O4^{iii}	0.95 (6)	1.77 (6)	2.711 (3)	174 (5)
C8—H8···O21^{i}	0.94 (3)	2.39 (3)	3.178 (3)	141 (2)

Symmetry codes: (i) $1 - x, y, \frac{1}{2} - z$; (ii) $x - \frac{1}{2}, \frac{1}{2} - y, z - \frac{1}{2}$; (iii) $\frac{1}{2} - x, \frac{1}{2} - y, 1 - z$.

Data collection: CAD-4F software. Cell refinement: CAD-4F software. Data reduction: *ENPROC* (Rettig, 1978). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *Stereochemical Workstation* (Siemens, 1989). Software used to prepare material for publication: *SHELXL*93.

The authors thank Marion Merrell Dow Research Institute, Cincinnati, Ohio, for the sample of 5,7-dichlorokynurenic acid and the Medicinal Research Council of Canada (grant MA 8087 to PWC) for financial support.

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: FG1216). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1997). C**53**, 742–744

2,3-Di-*O*-benzoyl-1-*O*-*p*-nitrophenyl-6-*O*-pivaloyl-4-*O*-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-2′-*N*-phthalimido-β-D-1′-glucopyranosyl)-β-D-glucopyranose

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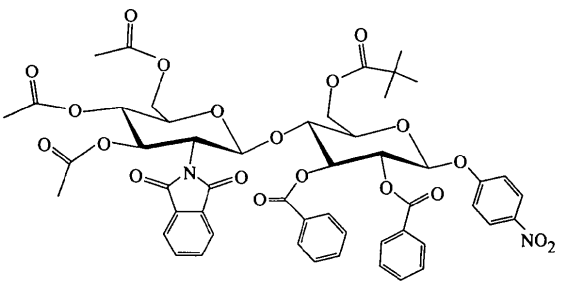
Abstract

The title compound, $C_{51}H_{50}N_2O_{20}$, is an intermediate in the synthesis of a substrate to be used in enzymological studies of lysozyme. It was synthesized *via* a trichloroacetimidate coupling of 2,3,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-1-trichloroacetimidate-β-D-glucopyranoside and *p*-nitrophenyl 2,3-di-*O*-benzoyl-6-*O*-pivaloyl-β-D-glucopyranoside. Both glucose rings adopt chair conformations with one described as $^1C_4$ and the other as $^5C_3$. Atoms C1 and C4 are at distances of 0.727 (4) and −0.652 (4) Å, respectively, and O5′ and C3′ are at distances of 0.713 (4) and −0.555 (5) Å, respectively, from their chair planes.

Comment

In the course of kinetic-isotope-effect method development for lysozyme, we initiated a flexible synthetic route to aryl disaccharide glycosides which would afford site-specific labelled isotopomeric products. We employed the trichloroacetimidate method (Grundler & Schmidt, 1985) to couple 2,3,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-1-trichloroacetimidate-β-D-glucopyranoside with *p*-nitrophenyl 2,3-di-*O*-benzoyl-6-*O*-pivaloyl-β-D-glucopyranoside to afford the desired title compound, (1), in 49% yield. Though the trichloroacetimidate couplings of gluco-configuration glycons are known to afford the β anomer as the major product (Grundler & Schmidt, 1985), the ambiguous spectroscopic data resulted in the need for a crystal structure determination to confirm the stereochemistry of the newly formed glycosidic linkage.



(1)

The anisotropic displacement-ellipsoid drawing of the title compound, (1), with the atom-labelling scheme is shown in Fig. 1. The absolute configuration of (1) was assigned using the knowledge of the stereochemistry of its synthetic precursor. Each of the non-H substituents on the ring is in an equatorial position. Those on C1,

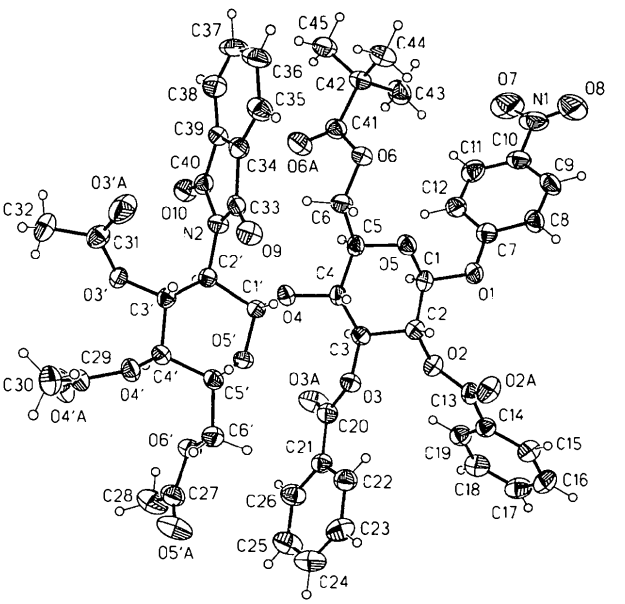


Fig. 1. The molecular structure of (1), with 50% probability ellipsoids, showing the atom-numbering scheme.